CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
DP150065

Project Title:
Development of a novel K-Ras therapeutic

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
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Entity:
The University of Texas Health Science Center at Houston

Lay Summary:

Ras proteins are small molecular switches located on the inside of the limiting cell membrane, called the plasma membrane. In the “ON” state, Ras proteins relay signals from outside of the cell to the cell nucleus that instruct the cell to grow and divide. Cancer cells acquire mutations that permanently lock Ras proteins in the “ON” state. These mutations therefore lead to unregulated cell division resulting the growth of a tumor. Ras mutations have been found in approximately 20% of all human tumors. The major clinical problem is with a form of Ras called K-Ras that is mutated in more than 90% of pancreatic cancers, 50% of colon cancers and approximately 25% of non-small cell lung cancers. The discovery of drugs to inhibit K-Ras is therefore of vital importance if we are to successfully treat this group of cancers. However, no anti-K-Ras drugs have yet been developed. K-Ras must be plugged into the plasma membrane in order to relay signals. If we simply remove the mutant K-Ras switch from the plasma membrane, it can no longer drive cell division and tumor growth. Using a novel assay developed in our laboratory we have identified chemical compounds that prevent K-Ras from associating with the cell membrane. One of these compounds, fendiline, potently inhibits the proliferation of cancer cells that express mutant K-Ras. The purpose of this project is to improve the K-Ras inhibitor function of fendiline by modifying the molecule and synthesizing new chemical derivatives. These new compounds will be tested for their potency and efficacy as anti-K-Ras drugs in cells as well as in mice with pancreatic cancer. These studies will lead to the identification of one or more potent anti-K-Ras drugs that are ready for clinical
evaluation in patients with pancreatic cancer.